Kindly amend the application as follows*:

IN THE CLAIMS

Please cancel claim 80, without prejudice.

Kindly amend the claims as follows:

1. (Amended) A crosslinked protein crystal, said protein crystal being crosslinked with a multifunctional crosslinking agent and said protein crystal being capable of controlled dissolution from insoluble and stable form to soluble and active form upon a change in the environment surrounding said crystal, said change being selected from the group consisting of: change in temperature, change in pH, change in chemical composition, change from concentrate to dilute form, change in shear force acting upon the crystal and combinations thereof.

17. (Amended) A crosslinked protein crystal, said protein crystal being crosslinked with a multifunctional crosslinking agent and said protein crystal having a half-life of activity under storage conditions which is greater than at least 2 times that of the soluble form of the protein that is crystallized to form said crystal that is crosslinked and activity similar to that of the soluble form of the protein under conditions of use.

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* Applicants have attached hereto Appendix A, which illustrates the claim amendments in the bracket and underline format.

18. (Amended) A crosslinked protein crystal, said protein crystal being crosslinked by a multifunctional crosslinking agent and said protein crystal being capable of releasing its protein activity at a controlled rate upon exposure to a change in the environment surrounding said crystal, said change being selected from the group consisting of change in pH, change in solute concentration, change in temperature, change in chemical composition, change in shear force acting upon the crystals and combinations thereof.

31. (Amended) The crosslinked protein crystal according to any one of claims 1, 17 or 18, wherein said protein is selected from the group consisting of hormones, antibodies, inhibitors, growth factors, trophic factors, cytokines, lymphokines, toxoids, growth hormones, nerve growth hormones, bone morphogenic proteins, toxoids and nutrients.

39. (Amended) A protein delivery system, said system comprising crosslinked protein crystals according to any one of claims 1, 17 or 18 and a delivery device.

48. (Amended) A pharmaceutical controlled release formulation comprising a crosslinked protein crystal, said protein crystal being crosslinked by a multifunctional crosslinking agent

and said crystal being substantially insoluble under storage conditions and capable of releasing its protein activity *in vivo* at a controlled rate.

54. (Amended) A method for producing crosslinked protein crystals comprising the step of reacting protein crystals in a slurry with a first multifunctional crosslinking agent, or a first multifunctional crosslinking agent and at least a second multifunctional crosslinking agent, under conditions sufficient to induce crosslinking of said crystals to the extent that the resulting crosslinked crystals are characterized by the ability to change from insoluble and stable form to soluble and active form upon a change in their environment, said change being selected from the group consisting of change in temperature, change in pH, change in chemical composition, change from concentrate to dilute form, change in shear force acting upon the crystals and combinations thereof.

55. (Amended) A method for producing crosslinked protein crystals comprising the step of reacting protein crystals in a slurry with a first multifunctional crosslinking agent, or a first multifunctional crosslinking agent and at least a second multifunctional crosslinking agent, under conditions sufficient to induce crosslinking of said crystals to the extent that the

resulting crosslinked crystals are characterized by a half-life of activity under storage conditions which is greater than at least 2 times that of the soluble form of the protein that is crystallized to form said crystals that are crosslinked and activity similar to that of the soluble form of the protein under conditions of use.

56. (Amended) A method for producing crosslinked protein crystals comprising the step of reacting protein crystals in a slurry with a first multifunctional crosslinking agent, or a first multifunctional crosslinking agent and at least a second multifunctional crosslinking agent, under conditions sufficient to induce crosslinking of said crystals to the extent that the resulting crosslinked crystals are characterized by being capable of releasing their protein activity at a controlled rate upon exposure to a change in their environment, said change being selected from the group consisting of change in pH, change in soluble concentration, change in temperature, change in chemical composition, change in shear force acting upon the crystals and combinations thereof.

67. (Amended) The method for producing crosslinked protein crystals according to any one of claims 54, 55 or 56, wherein said crosslinking agent is glutaraldehyde at a concentration of 0.0076% to 0.5% in the slurry and wherein the conditions sufficient to induce crosslinking include reacting

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protein crystals with a crosslinking agent for a period of time between about 3 minutes and about 120 minutes.

68. (Amended) The method for producing crosslinked protein crystals according to claim 67, wherein said crosslinking agent is glutaraldehyde at a concentration of 0.005% in the slurry and wherein the conditions sufficient to induce crosslinking include reacting protein crystals with a crosslinking agent for a period of time between about 10 minutes and about 30 minutes.

A7 cancel.

70. (Amended) The method for producing crosslinked protein crystals according to any one of claims 54, 55 or 56, wherein said crosslinking agent is glyoxal at a concentration of 0.01% to 1% in the slurry and wherein the conditions sufficient to induce crosslinking include reacting protein crystals with a crosslinking agent for a period of time between about 30 minutes and about 60 minutes.

A8 cancel.

71. (Amended) The method for producing crosslinked protein crystals according to any one of claims 54, 55 or 56, wherein said crosslinking agent is octanedialdehyde at a concentration of 0.05% to 1% in the slurry and wherein the conditions sufficient to induce crosslinking include reacting protein crystals with a crosslinking agent for a period of time between about 30 minutes and about 16 hours.

72. (Amended) The method for producing crosslinked protein crystals according to claim 71, wherein said crosslinking agent is octanedialdehyde at a concentration of 1% in the slurry and wherein the conditions sufficient to induce crosslinking include reacting protein crystals with a crosslinking agent for a period of time between about 1 hour and about 3 hours.

73. (Amended) The method for producing crosslinked protein crystals according to any one of claims 54, 55 or 56, wherein said crosslinking agent is succinaldehyde at a concentration of 1% in the slurry and wherein the conditions sufficient to induce crosslinking include reacting protein crystals with a crosslinking agent for a period of time between about 30 minutes and about 3 hours.

74. (Amended) The method for producing crosslinked protein crystals according to any one of claims 54, 55 or 56, wherein said first crosslinking agent is epoxide at a concentration of 0.01% to 4% in the slurry and said second crosslinking agent is glutaraldehyde at a concentration of 0.1% to 0.2% in the slurry and wherein the conditions sufficient to induce crosslinking include reacting said protein crystals with said first crosslinking agent for a period of time between about 1 hour and about 72 hours and reacting said protein crystals with said

second crosslinking agent for a period of time between about 1 hour and about 5 hours.

75. (Amended) The method for producing crosslinked protein crystals according to claim 74, wherein said first crosslinking agent is epoxide at a concentration of 0.01% in the slurry and said second crosslinking agent is glutaraldehyde at a concentration of 0.1% in the slurry and wherein the conditions sufficient to induce crosslinking include reacting said protein crystals with said first crosslinking agent for about 5 hours and reacting said protein crystals with said second crosslinking agent for about 1.5 hours.

81. (Amended) The method for producing crosslinked protein crystals according to any one of claims 54, 55 or 56, wherein said enzyme is selected from the group consisting of hydrolases, isomerases, lyases, ligases, transferases and oxidoreductases.

REMARKS

Applicants have amended claims 1, 17, 18, 54-56, 81 and the claims that depend therefrom, to specify that the crosslinked protein crystals of and produced by the methods of this invention are crosslinked by a multifunctional crosslinking agent. Support for this amendment can be found throughout the specification, for